

Collaborative strategies for the search of 3D targets in molecular environments

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Abstract—Collaborative Virtual Environments introduce new working methods allowing for the association of several experts in the same problem-solving process. These new platforms have the potential to improve the processing of complex environments with large amounts of data and require different skills. This article proposes the study of a synchronous and colocated approach for molecular design tasks.

The aim of this work is to highlight the different working strategies and simultaneous interaction approaches that emerge according to different tasks and humans factors. Based on these working strategies, we propose to investigate the contribution of collaborative configuration of work according to different efficiency criteria (such as execution time and energy). Finally, this study will highlight some issues related to conflict of actions, concurrent access, awareness and communication processes.

I. INTRODUCTION

Collaborative Virtual Environments (CVE) play today an important role in the evolution of working methods by enabling several users to create, exchange, manipulate and disseminate information in shared spaces. This approach enables the capitalization of creative abilities and the association of complementary skills.

After exploring the potential of CVE in virtual prototyping and assembly (e.g., CAD, Digital Product Development Product Lifecycle Management) [1]; and in review of collaborative projects (e.g., prospecting for geological resources) [2], CVE research now allow to process, analyse and manipulate collaboratively complex masses of data such as those used in Fluid Mechanics and in simulations of Dynamic Systems. These environments are characterized by a large dataflow to analyse, and present multiple Degrees of Freedom (DoF) for manipulation. CVE play a strategic role by enabling a problem's complexity to be shared between several partners. This new working configuration significantly decreases the individual cognitive workload, as well as makes the process more robust and reliable by introducing additional skills and knowledge in the same problem-solving process [3].

Among complex environments, molecular design and Docking simulation are suitable applications for the emergence of CVE approaches. These research areas generate an interest within the scientific and industrial communities and represent a considerable challenge in the fields of pharmacology and biotechnology. Current tools of molecular design allow the prediction of new molecular complexes and thus the development of new drugs and medicines. However, the analysis of

relevant molecules is a complex task for biologists, both from the point of view of the involved physical phenomena and the topological complexity. It requires the interpretation and manipulation of a high level of DoF and physical parameters. Furthermore, these tasks are based upon several areas of expertise (e.g., modelling expertise for the structural and flexibility features, and biological expertise for the functional features).

Several human-centered approaches [4] [5] [6], through immersive and multimodal techniques, were investigated to improve usual computer-based analysis solutions [7]. Empirical and experimental evaluations have clearly shown the role of the human operator, through Virtual Reality (VR) based approaches, in the improvement of search and analysis processes for small molecules. The skills of the biologist combined with a real-time perception of physicochemical and topological properties enables a continuous supervision process, easing the interactive restriction of the search space and filtering wrong solutions [6].

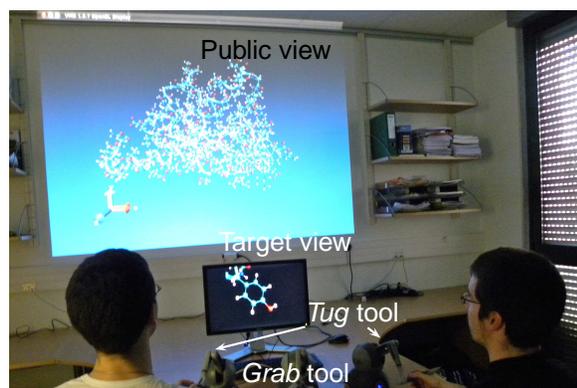
The recent developments in molecular modelling enable real-time manipulation of large proteins [8]. These new models integrate several scales of deformation corresponding to different levels of biological approximation. This complete representation significantly increases the complexity of the molecular manipulation problem by adding a high number of DoF and parameters to the initial problem. This new complex context with its large number of parameters to manage and artefacts to manipulate, goes beyond the abilities and the skills of a single human expert. Therefore, it seems necessary simultaneously to introduce two or more experts in the docking process to analyse, explore and find a docking configuration for these huge molecules.

Since the emergence of protein databases during the '70s and '80s, different solutions allowing several biologists to simultaneously study and manipulate molecules and chemical structures were developed. However, these approaches concern a high level asynchronous manipulation without a direct interaction between involved participants. This constraint is linked, on the one hand, to the complexity of the large molecular structures, and on the other hand, to the physical distance between partners in the case of remote collaboration. These two features have a direct consequence on communication, exchange and concurrent interaction mechanisms in CVE which limit the efficiency of closely coupled manipulation.

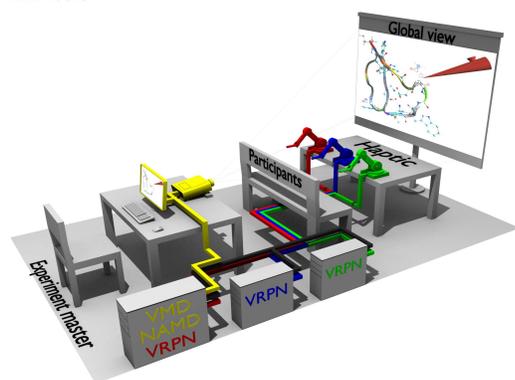
This article investigates synchronous and colocated CVE for a molecular manipulation task (see Figure 1a). In particular, the study reported here focuses on the search process (see Figure 2b) which is a critical step during the deformation and

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(a) Illustration of the CVE environment with public and target view and tools



(b) Schema of the experimentation room

Figure 1: Synchronous and colocated CVE for molecular design and assembly: the platforms connects desktop based biologists' working environment.

the assembly of molecules. The aim of this work is, on the one hand, to highlight the role and the contribution of CVE for the improvement of closely coupled collaborative tasks, and on the other hand, to analyse the main limits and the constraints of CVE in order to propose several issues and perspectives to setup efficient CVE for interactive molecular manipulation tools.

The article is organised as follows: section II presents a literature review of existing work and platforms on collaborative molecular design and analysis. section III develops the investigated problem and the contribution of the study reported here. section IV presents the experimental study of exploration and search of residues in biological environment. section V develops the results and discusses the contribution of CVE for the fulfilment of the tasks. Finally, section VII summarises the contribution of CVE and presents some issues and prospects for molecular design based CVE.

II. STATE OF THE ART

Early work in collaborative study of molecular structures and chemical components enabled several scientists to view and interactively edit a shared molecular model through a standard mouse [9]. The client application is based on common web technologies (VRML, Mosaic World-Wide Web browser, etc.) and allows the scientist to communicate through video

conferencing and shared whiteboards (SGI InPerson). In 1998, Bourne improved the concept and proposed MICE (Molecular Interactive Collaborative Environment) [10]. This platform integrates three main components: (1) a Molecular Scene Description Language (MSDL), a language allowing the direct exploitation of standard data files in shared environments; (2) a visualisation tool, with several navigation and rendering possibilities; and (3) a software for collaborative access to molecular scenes, a set of protocols for scene synchronisation and the management of manipulations (of 3D structures) in shared environments. MICE is also based on common web technologies (JAVA/VRML). This application concerns mainly the distant manipulation of molecules for structural characterisation. Each expert manipulates regions separately without direct interaction with partners.

[11] proposed the first attempt to integrate immersive Virtual Reality approaches in collaborative molecular design. The proposed platform allows two biologists remotely to explore and interact with the same molecule through immersive visualisation feedback and passive interaction interfaces (Wand interface). Kriz in [12] improved the initial approach by (1) using an immersive CAVE; (2) using 3D avatars to represent several collaborators; and (3) allowing the display of information about 3D structures and partners. Kriz also proposed a desktop version of the collaborative platform. In 2005 several projects on collaborative molecular design were presented. First, Ghadersohi in [13] presented a generic collaborative platform for scientific visualisation. The proposed solution allows full immersion through a CAVE system and supports common desktop and laptop stations. In [13], the validation of the proposed concept was carried out on elementary manipulation of biological structures through a sequential scenario. Also in 2005, [14] presented his work on inter-referential awareness for collaborative molecular modelling. He also developed several approaches for sharing views between collaborators and proposed an original concept for the management of simultaneous molecule manipulation through a passive approach (3D bounding-box). Chastine carried out his work in both fully immersive and augmented reality environments.

The eMinerals project is presented in [15]. eMinerals includes a complete large-scale collaborative solution (dozens of collaborators) for the visualisation and design of complex molecules. With this solution, the collaborators are organised in groups between the different laboratories. Each group is expert in a specific domain (experimental, final user, etc.). The global platform integrates three main shared components: (1) a compute grid, for calculations; (2) a data grid, to manage the shared 3D structures; and (3) a collaborative grid, allowing for sharing of information, communication and management of interactions between collaborators. It should be noted that eMinerals is a desktop-based solution. In the same category of collaborative solutions (i.e., desktop based), a commercial solution is available today: Chimera Collaboratory Extension [16]. This solution is a plug-in for the Chimera Molecular Modelling platform that allows the use of several collaborative tools. This solution allows several collaborative scenarios (e.g. synchronous or asynchronous) on a widely used molecular modelling platform.

More recently, the Theoretical and Computational Biophysics Group (TCBG) at the University of Illinois proposed the Biological Collaborative Research Environment (BioCoRE) [17]. BioCoRE is a unified web-based collaborative environment designed to facilitate work between biomedical researchers located at the same or geographically distant sites. Users create project groups and can then share molecular views, messages, files, and more among the members of their projects. BioCoRE supports four basic types of activities: (1) utilizing a wide range of computational tools (VMD, NAMD, etc.); (2) keeping records; (3) communicating with collaborators; and (4) writing multi-authored articles and reports. This functionality has been grouped into the following components of BioCoRE: Workbench, Notebook, Conferences and Documents.

Finally, the Bioinformatics group at Johnson & Johnson Pharmaceutical Research & Development developed a real-time immersive data visualisation theatre environment to explore interactions of candidate drug molecules with target receptors [18]. This platform enables an interdisciplinary collaboration (mainly briefing and meeting) between scientists from several research fields.

Beyond molecular design and manipulation, several studies investigated collaborative concepts for common tasks in Virtual Environments. Ruddle et al. [19] investigated the collaboration for the *piano movers' problem*. This study highlights the reduction of collisions with the environment through additional working strategies. However, there is no improvement of execution time. In fact, the communication between the two partners counterbalances the gain of execution time. Groten et al. [20] study the role of collaboration to carry some elementary objects presenting several weights. The results of this study revealed improvement of gesture accuracy, and highlighted working strategies to share the workload between the two partners. Basdogan et al. [21] and Reed et al. [22] study the role of sensorial communication to improve the gesture coordination for elementary manipulation tasks. This study shows the role of the *feedthrough* channel for the indirect communication between partners. Finally, Tang et al. [23] study group activities in term of collaborative coupling strategies in the context of tabletop collaboration. This research highlights different coupling styles according several variables (proposed tools, physical arrangement of partners, etc.).

III. AIM OF THE STUDY

As developed in the state of the art, CVE platforms today enable biologists to work in the same virtual space according to different spatial (distant vs. colocated) and temporal (synchronous vs. asynchronous) configurations. However, this work does not investigate mechanisms, contribution and roles of CVE for the fulfilment of complex molecular manipulation and analysis tasks. Otherwise, the existing research in molecular design mainly proposes lowly coupled collaboration strategies without a direct interaction between partners in the virtual environment. Furthermore, the state of the art shows research highlighting the role of CVE for the improvement

of common tasks and shows the important factors to consider and to investigate to setup efficient CVE (e.g. improved communication, collaborative strategies, coordination of actions, etc.).

Based on these results, we have conducted a series of studies to investigate and characterize collaborative work for closely coupled tasks in molecular environment to understand the contribution of this new configuration of work for the fulfilment of complex tasks. Furthermore, this study will highlight specific constraints and limitations of CVE for molecular manipulation (e.g. communication, conflicting actions, etc.) which must be considered for the design of efficient molecular manipulation in CVE.

A. Investigated task: search of targets

The context of the proposed study is the docking of huge molecules. This process involves a complex analysis and manipulation procedures and is based on a hierarchical decomposition of the levels of complexity of the molecule (see Figure 2). Conventionally, biologists consider three main levels of modelling according to a top-down synthesis:

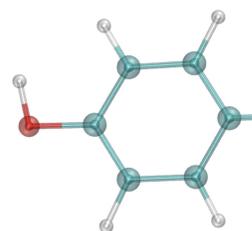
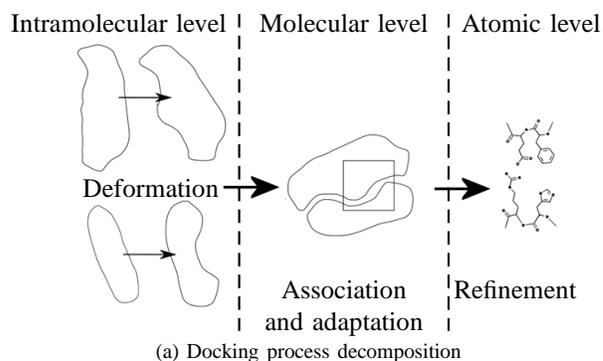


Figure 2: Main steps of docking process with example of an elementary structure to manipulate.

- **Intramolecular level for macromolecular deformation** This level of modelling concerns the large amplitude displacements which describe the conformational changes of molecules. The main objective is to deform the two macromolecules and press one of them onto the other. Afterwards, this global deformation will enable several associations at the molecular level.
- **Intermolecular level for molecular anchoring and induced deformation** This modelling level consists in

associating the molecules resulting from global macromolecular deformation. In fact, the combination of the two macromolecules in the previous stage produces several interfaces which must be matched according to several criteria, such as surface complementarities, geometrical contact between molecules, or electrostatic and Van der Waals attraction-repulsion forces.

- **Refinement of the resulting binding pose** This level of Docking exploits the refinement of the molecular model by focusing on important interactions such as salt-bridges, hydrophobic effect and hydrogen bonding. The refinement consists in manipulating the relative rotation-translation locally for a coarse or fine adaptation.

Even if these procedures occur at different scales, they are based on a common set of elementary subtasks in the biologist's frame of reference. We can define some of them as follows:

- **Search of targets** This task consists in finding a target (residues, structures, atoms, region) according to several criteria (articulation/joint, energy score, shape, hydrophilic/hydrophobic regions, etc.).
- **Selection of targets** This task consists in accessing and holding (with a mouse or haptic arm) the found target. This step prepares the manipulation or deformation procedure.
- **Deformation of structures** This task consists in a deformation of structures (intermolecular, intramolecular or atomic levels) to minimize the energy criterion.
- **Evaluation of energy** This task consists in calculating different terms of the potential energy (surface complementarities/collision, electrostatic and van der Waals attraction-repulsion, etc.) of a given interface or structure to evaluate the corresponding stability and balance.

Among these subtasks, we propose here to investigate the first step of the described procedures [24]: the *search of targets*. In fact, this subtask enables the definition of critical zones (manipulation zone, flexible zone, etc.) which define and impact the future operations.

B. Collaborative context

Based on the Ellis's space-time continuum [25] (distance and time dimensions) and the different functions of collaborative spaces [26] (brainstorming, briefing, review, etc.), we propose to investigate the *collaborative activity* function (search of targets) in a synchronous and colocated configuration. All experimented targets were defined to enable a closely coupled collaboration between partners according to various mechanisms (e.g. collaborative search, collaborative manipulation, collaborative selection). This configuration of work should require both an interactive coordination of actions and a mutual active supervision between involved experts during the manipulation process to avoid some critical conformations. The aim of these different scenarios is twofold: first, highlighting novel working strategies allowing the synchronous co-realisation of critical tasks requiring the combination of several skills, and second, investigating mechanisms, contribution and roles of CVE for the fulfilment of various complex tasks.

C. Investigated factors

Two main factors were investigated in this study. First, the impact of the number and skill of the involved partners on the achievement of the collaborative exploration and search processes. The aim of the study is to highlight, on the one hand, the effectiveness of task achievement according to the number of partners, and on the other hand, the evolution of the involved methods of work when experts with different skills work together. In fact, when we change from a single-user configuration to a multi-user configuration, the effectiveness of task achievement evolves in terms of execution time, manipulation precision or result's reliability. Therefore, it is important to analyse the contribution of collaborative configuration to the effectiveness criteria and to understand the evolution of working methods (e.g. energy, sequence of tasks) from a single-user to a multi-user configuration.

The second factor investigated in this study concerns the understanding of the working strategies that are involved. In fact, according to the level of complexity of the manipulated molecules, the group of partners involved and the fulfilled phases (see section IV-B for the navigation phases), several strategies of work should be established. According to some objective experimental results (e.g. working space, communication), we propose to analyse and highlight the main strategies used by the participants.

We can summarize these objectives in the following hypothesis:

- H1 Collaborative configuration improves the working efficiency.
- H2 Several working strategies should emerge.

IV. EXPERIMENTAL DESIGN

A. Hardware setup

Experiments were conducted on a collaborative platform coupling standard desktop workstations providing individual private views, with a large screen display, for the public and global view (see Figure 1a). This solution takes into account the existing working procedures of biologists (Desktop environment) while proposing an extension to CVE (e.g. public view with a large screen, several haptic arms for bimanual mode).

The rendering of the molecular environment was carried out with VMD [27]. This software enables the visualisation and the analysis of the results of molecular dynamics simulations in an interactive way. It proposes different graphic rendering of atoms, chains and several specific molecular structures. Elementary interactions with the molecular environment is possible through basic mouse devices or with 3D spaceballs for the rotation and translation of molecules or for the manipulation of several structures for instance.

For the biomolecular simulation the NAMD package [28] was used. This free-of-charge molecular dynamics simulation program allows efficient computation of interactions between atoms. NAMD program is able to calculate the evolution of a molecule in several molecular environments according to different levels of simulation and conditions (solvent, temperature, etc.). To enable the interactive simulation, the IMD

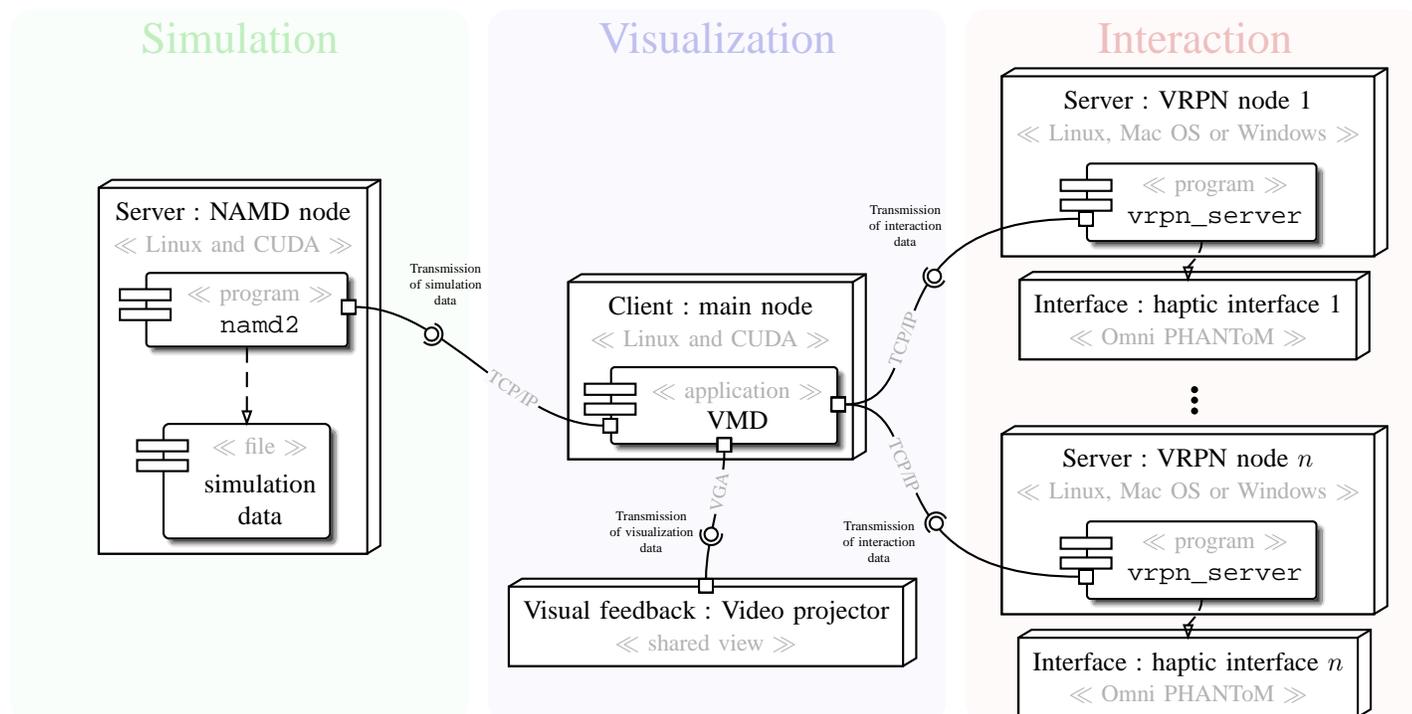


Figure 3: UML diagram of the software.

package [29] was used. This package is the software interface between VMD and NAMD (see Figure 3).

As mentioned above, the standard interaction with the molecular environment was achieved by a 2D mouse. However, this interaction approach has limits for the manipulation and for the interaction between users in the 3D space. For the proposed CVE, a set of 6 DoF (3 actives) haptic interfaces of type PHANToM Omni from SensAble was integrated. For this experiment three haptic interfaces were connected to VMD. The connection was achieved by VRPN [30]. To avoid several software and hardware limitations (e.g. Linux driver, VRPN limits) the haptic arms were connected to different computers. Thus, for each haptic arm, one machine was running with a VRPN server (Windows, Mac OS or Linux). The computer running VMD was the VRPN client synchronizing all information. It ran on Ubuntu 9.10. VRPN servers were executed on Windows XP or Linux. Figure 3 presents the global software architecture of the platform.

The visualization of the molecular environments was achieved with a HD video projector. This implies a common view and navigation function for all participants. The desktop screens were used in this experiment to display the targets to reach (such as the structures to search). The haptic interfaces were aligned in front of the main screen.

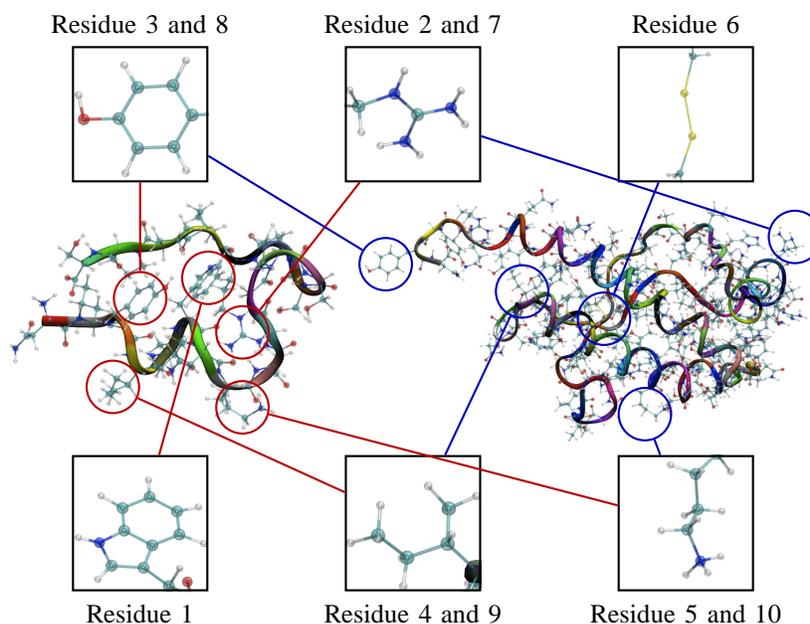
Finally, in order to analyse the communication process between participants. The audio of the experimental room was recorded. For this purpose, a microphone and the free audio processing software *Audacity* were used.

Figure 1b presents the collaborative platform.

B. Experimental protocol

1) *Independent variables:* Two main variables were investigated in this study. The first one concerns the number of participants. Two main working configurations were taken into account: (1) single participant; and (2) group of two participants. Since the experiment concern elementary search tasks, participants without specific skills (e.g. biologists, computer scientists, engineers) completed the tasks.

The second factor concerns the level of complexity of the task. This factor is linked to the different features of the manipulated molecules (shape, size, number of atoms, etc.) and the specified structures to find. Two molecules with different sizes were used: the TRP-CAGE [31] with 304 atoms and the Prion [32] with 1776 atoms (see Figure 4a). As was mentioned above, the context of this experiment is the search of noticeable biologic structures in molecules (see Figure 2b). Thus, the participants' task was to find ten different structures: five on the small TRP-CAGE molecule and five on the big Prion molecule. To determine that the task was completed, once the structure was found, the participant had to catch one atom of the structure with the *tug* tool and pull it out of the molecule according to a defined configuration. Table 4b summarizes the different features of the experimented structures. Each feature corresponds to a specific variable of the task complexity. The first column indicates the geometrical position of the structures in the molecule. Extern and intern means that the structure is respectively in the periphery or in the middle of the molecule. External structures involve a simple peripheral exploration of the molecule. However, internal structures involve complex search processes including the deformation of the molecule. The second column indicates the geometrical structure of the pattern. Three shapes are



(a) Repartition of patterns on TRP-CAGE and Prion molecules

Pattern	Position	Form	Color	Similar	Pattern	Position	Form	Color	Similar		
TRP-Cage (304 atoms)	1	Intern	Circle	8 C, 1 N	No	Prion (1776 atoms)	6	Intern	Chain	2 C, 2 S	No
	2	Intern	Star	1 C, 3 N	No		7	Extern	Star	1 C, 3 N	No
	3	Intern	Circle	6 C, 1 O	No		8	Extern	Circle	6 C, 1 O	No
	4	Extern	Chain	4 C	No		9	Intern	Chain	4 C	Yes
	5	Extern	Chain	4 C, 1 N	No		10	Intern	Chain	4 C, 1 N	Yes

(b) Involved factors in the complexity of the molecules (Carbon, Oxygen, Nitrogen and Sulfur)

Figure 4: Repartition of patterns to find and corresponding complexity factors.

proposed: circle, chain and star. The circle structure presents a rigid configuration with small deformations which makes them easy to find. The chain and the star structures deform easily under the effect of the rest of the molecule and external forces. Thus, these structures are difficult to find. The third column concerns the colour of the concerned structures. In fact, each pattern has a combination of colours according to the involved atoms. The association between atoms and colours are generally the same in the great majority of biologic sharewares. The most present atoms are hydrogen and carbon with respectively white and green colours. In second position, we find nitrogen and oxygen with respectively blue and yellow colours. The rarest atom is sulfur with a yellow colour. Hydrogen is not indicated in the table because it is included in all the patterns. It is obvious that patterns with rare atoms (such as sulfur) are easier to find than patterns with common atoms (hydrogen and carbon). The last column concerns the level of presence of similar structures in the molecule (similar number of atoms, similar colours, etc.). For instance, patterns with 3 carbons and 1 nitrogen and patterns with 3 carbons, 1 nitrogen and 1 oxygen are visually very similar. Moreover, in this experiment, similar patterns are more present than selected

structures (in each case for the Prion).

2) *Interaction tools*: Two ways of interacting with the molecular environment were proposed. The first tool, called *grab* in VMD, allows the positioning and the orientation of the manipulated molecules. This tool does not influence the simulation, it mainly concerns navigation and exploration procedures.

The second proposed tool, called *tug*, allows the manipulation of and the interaction with the atoms. Once the atom is selected, it is then moved according to a force that is proportional to the distance between the atom and the Virtual End-Effectors (VEE). The corresponding atomic interaction and applied force were displayed on the haptic interface. Thus, the participants were aware of the intensity and the direction of the force they apply.

These two interaction tools (*grab* and *tug*) were shared on three haptic interfaces. The *grab* tool was linked to the middle haptic arm in order to be accessible for the two participants. Thus, only one participant was able to manipulate the point of view of the molecule at any time. The *tug* tool was linked to the two other haptic arms to allow both participants to manipulate the molecule simultaneously (see Figure 1b).

3) *Participants*: 24 participants, 4 women and 20 men aged between 21 and 54 years old completed the experiment. The participants have different skills and work in different research fields.

In order to compare collaborative work and single user configuration, the participants completed the task 2 times: alone (24 participants) and in pairs (12 pairs of participants). The task was exactly the same for the two configurations. However, in the pair configuration, only one of the two participants could manipulate the point of view through the *grab* tool. The order in which the two configurations (single vs. group) were alternated across participants.

4) *Experimental procedure*: The experiment is based on the Bowman navigation process [33]. It includes three levels of strategy [34]:

- **Exploration** there is no specific objective. The participant can explore the virtual environment without explicit modifications. This step allows the construction of a mental map of the environment and its corresponding features.
- **Searching** Once the objective defined, the participants have to find the target. Two scenarios are possible : (i) Unknown target and (ii) Defined target
- **Positioning** This task involves precise movements to adjust the point of view. This step precedes any manipulation or modification task.

According to this navigation process, participants were first asked to explore the molecule during 1 minute. This step implies the use of the *grab* tool only, without direct interaction with the molecule. During this step, the patterns to find were not defined yet. Moreover, in collaborative configurations, the participant who lead the exploration process (*tug*) was chosen before starting. Once the exploration step was completed, the search task began by displaying the series of ten patterns. No predefined strategies were proposed to nor imposed on the participants. Each pair of participants was free to adopt what they considered the most suitable strategy. Finally, the task was achieved when the pair of participant had found and selected the specified pattern together simultaneously (with the VEE/*tug* tool). The participants were asked to pull the patterns outside the molecule according to defined configurations. The different measures concerns the searching and positioning steps. For single participants, the task was similar. However, the exploration step did not require the specification of a leader and the adjustment step involved only one user.

5) *Dependant variables and measures*: Several measures were collected for each condition. First, objective measures. The corresponding variables are:

- Execution time: total and for each step (search step and selection step)
- Verbal communication duration: total and for each step
- Position and trajectory of VEE
- Distance between working spaces
- Applied force during the manipulation

Based on these objective measures other measures will be derived in the analysis section.

In addition to these objective measures, we propose to evaluate the level of affinity between partners of the same

group. This measure reflects the respect and willingness to work together. It is based on a form, inspired from the work of Oren [35], completed by the supervisor in the beginning of the experiment. The form includes several criterions (e.g., distance between offices, hierarchical relation, etc.) evaluated with a 5-points Likert's scale [36].

Finally, a questionnaire was proposed to the participants at the end of the experiment. Two different questionnaires were presented: one for single participants and one for pairs of participants. The questionnaire concerned the subjective evaluation of the different features of collaborative work compared to single configuration (e.g. perceived efficiency, perceived partner contribution, communication) with a 5-points Likert's scale [36].

6) *The questionnaire*:

- In which configuration do you think that you are more efficient: single or collaborative?
- During the collaborative task, do you think that you have helped or penalized you partner?
- Who lead the collaboration: you or your partner?
- What was the nature of communication with your partner: verbal, gestural or virtual (VEE)?

V. EXPERIMENTAL RESULTS AND DISCUSSION

This section presents the experimental results showing the strategies involved, the new methods of work, and the contribution of collaboration to the improvement of the efficiency according to the examined factors (e.g. complexity, number of participants). Furthermore, we highlight the configurations in which collaborative work presents limitations for the fulfilment of the tasks (subtasks and complete tasks). Finally, we highlight several limitations on communication and interaction for this new working method.

A. Improvement of working efficiency

An ANOVA conducted on execution time with two factors: the complexity of the molecules and the number of participants revealed a significant effect of the complexity of the molecules ($F(1, 11) = 71.02, p \ll 0.01$), a significant effect of the number of participants ($F(1, 11) = 6.10, p < 0.05$), and no significant interaction between these two factors ($F(1, 11) < 1, ns$) [24].

With respect to the number of participants, the collaborative configuration improves task fulfillments compared to single user configurations. It should be noticed that the fulfillment of collaborative tasks includes communication between participants (e.g. verbal, gestural), while single user configuration does not include. The detail of these results is developed in next sections.

1) *Overall execution time*: Figure 5 shows the total execution time for all patterns including collaborative and single participant configurations. First, these results highlight the different levels of difficulty for finding the different patterns. Thus, some structures are more difficult to find than others. Indeed, post-hoc tests [37] conducted on the 10 different patterns revealed a significant difference between the group of patterns (6, 9, 10) and the group (1, 2, 3, 4, 5, 7, 8) (all

p -values < 0.01 for comparisons across these groups). Thus, patterns 6, 9 and 10 can be considered more complex than the other structures. The difficulty to find the different patterns is linked to the complexity of the factors developed above (see Table 4b).

The small size of the TRP-Cage molecule presents a limited number of patterns to examine. Thus, after a rapid exploration of the molecular structure, participants can rapidly find the presented patterns thanks to the geometrical structure and the colour features of the patterns. Pattern 4 is a little less difficult to find due to its special colour composition.

The large Prion molecule presents a more complex structure with high number of residues and internal structures. After a peripheral exploration, participants identify some noticeable external patterns (patterns 7 and 8). However, they need to deform the molecular structure to find internal patterns (patterns 6, 9 and 10). In this case, the execution time is longer and is linked to the different features of the patterns (e.g. position, particular geometrical structure, colour).

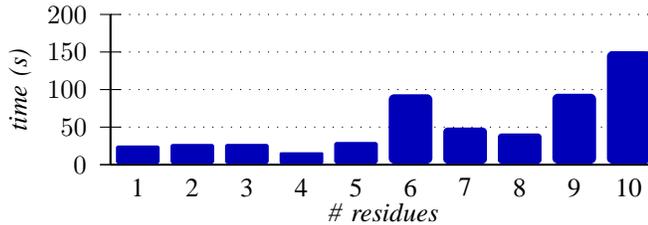


Figure 5: Mean execution time including collaborative and single participants configurations. This result highlights the different levels of difficulty for investigated tasks.

2) *Execution time for single and collaborative configurations*: Figure 6 compares the execution time of collaborative and single partner configurations. The first five patterns induce a low execution time for both collaborative and simple participant configurations. In fact, the small size of the TRP-Cage molecule presents patterns that are rapidly accessible. A small advantage for the collaborative configuration, without a significant difference, was observed.

For the Prion molecule, two cases can be distinguished. First, for patterns 6 and 9, a significant improvement of execution time for collaborative configuration was observed. A Duncan post-hoc test conducted on the group factor (single vs. group) and patterns factors (10 patterns) shows a significant difference between single participant and collaborative configurations for pattern 9 ($p \ll 0.01$) and pattern 6 ($p < 0.2$). These two patterns are internal structures with small differences with the rest of the residues of the molecule (Figure 8, pattern 9) or present some access difficulties (Figure 8, pattern 6). Thus, the collaborative configuration improves the working performance.

The three other patterns (patterns 7, 8 and 10) do not present significant differences between collaborative and single participant configurations ($p > 0.5$). The patterns 7 and 8 correspond to noticeable structures which are quickly identified (see Figure 8). The pattern 10 is an internal structure requiring an important search time (see Figure 8). The collaborative

configuration improves slightly the search step.

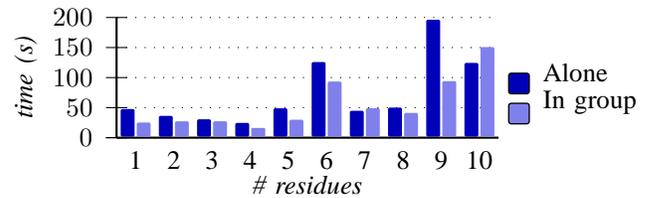


Figure 6: Mean execution time depending on the biologic structure to search according single and group configurations: Group configuration mainly improves tasks 6 and 9. The other tasks present no significant improvements.

3) *Execution time for search and selection steps*: As developed in the experimental procedure, the effective search process includes two main steps (see Figure 7): (1) the search step; and (2) the collaborative selection step (see section IV-B4). Based on the analysis of the verbal communication between the two partners, we have identified these two steps according to the time when one of the two partners identifies and finds the pattern (through a verbal indication). We consider that the rest of the time is assigned to the collaborative selection step.

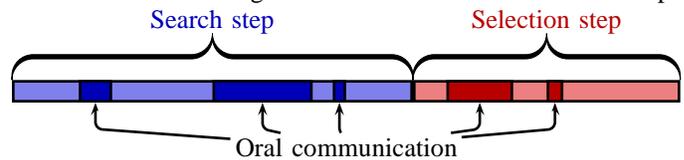


Figure 7: Search and selection steps and corresponding verbal communication.

The analysis of this measure highlights three configurations of time allocation (see Figure 8):

- No significant differences between search and selection execution times ($p > 0.05$); it concerns all patterns of the TRP-CAGE molecule and patterns 7 and 8 of the Prion molecule. As developed above, these configurations are too simple to induce differences (e.g. small molecule, external patterns, etc.) and the collaborative configuration does not increase the performance.
- Important search time with significant difference with selection time ($p < 0.05$); this configuration concerns patterns 9 and 10. These two patterns require a long period of deformation to highlight and explore internal structures. Once identified, partners can access and rapidly select the concerned pattern.
- Important selection time with significant difference with search time ($p < 0.05$); this configuration concerns the pattern 6. Partners rapidly identify the pattern involved. However, they take a long time to clear and unblock the complex structure to enable access to the concerned pattern.

4) *Execution time for slower and faster partners*: Figure 9 shows that there usually is a difference in efficiency between partners of the same pair (during individual experiments): there was always a fast partner and a slow partner. However, when participants work together, the global execution time converges to the minimum time of the two partners (best individual

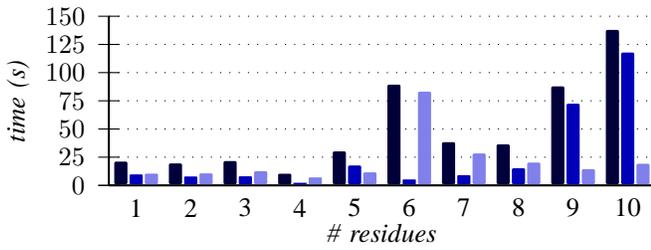


Figure 8: Mean search and selection time for collaborative configuration: The different tasks involves variables search and selection time according involved complexity factors (see Table 4b).

execution time). Collaborative work tends to improve the global efficiency of the group and improve performance of ineffective partners.

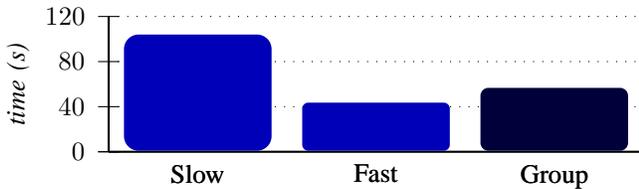


Figure 9: Pattern 9: Mean execution time for fast and slow participants for single configuration (blue columns) and corresponding mean execution for collaborative configuration (orange columns).

B. Working strategies

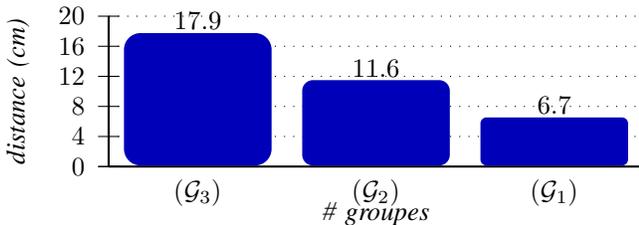


Figure 10: Average distances between the workspaces of the two partners: The distance between workspaces highlights three working strategies according several factors (e.g., affinity between subjects, verbal communication, applied force, execution time).

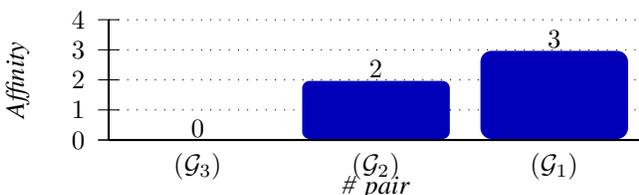


Figure 11: Level of affinity between participants: This measure is based on a form completed by the supervisor in the beginning of the experiment. The important scores mean that participants are close colleagues and the low score means that participants do not know each other.

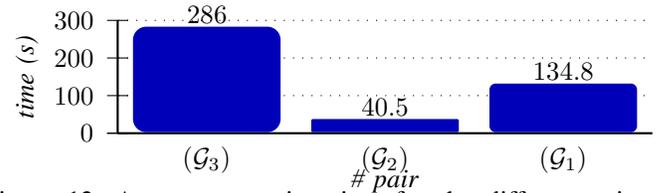


Figure 12: Average execution time for the different pairs: We observe that working on neighbouring regions present the most efficient execution time. Conversely, working in the same regions or at distant presents lower performances.

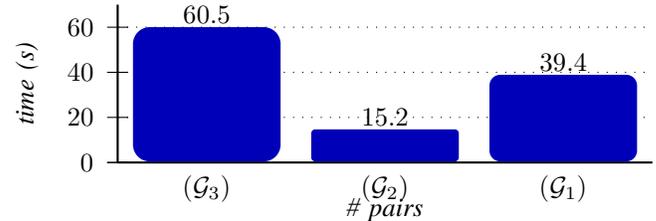


Figure 13: Total time of verbal communication: This measure includes the effective time of verbal exchanges.

An EM (Expectation-maximization) clustering approach, under the WEKA software, was applied simultaneously on the following measures [38] according the involved pairs:

- Average distance between workspaces of the two partners given in the world reference (the frame of reference of the haptic arm).
- Average execution times.
- Total time of verbal communication.
- Percentage of the verbal communication during the search and selection steps.
- Mean Applied force by the two partners.
- Difference of applied forces between the two partners.
- Level of affinity between partners.

The EM analysis highlights three groups of users developed in the following sections [39]. Figure 10, Figure 11, Figure 12, Figure 13, Figure 14 and Figure 15 summarize the results.

1) *Group 1*: From Figure 10, we observe that this group presents the smallest distance between the two workspaces of partners (distance < 8 cm). This distance is at the scale of a residue (real distance < 10 Å) which mean that the two partners worked frequently on the same residue. 2/3 of the pairs adopt this working strategy. From Figure 11, we observe that this configuration of work concerns partners with an important affinity. This group includes mainly close colleagues and friends. Figure 12 shows that the completion time for this group is on average intermediate compared to the two other groups (Groups 1 and 2). From Figure 13, we observe that the time of verbal communication is on average intermediate compared to the two other groups (Groups 1 and 2). Moreover, Figure 14 shows that this group dedicates more communication time for the search step than for the selection step ($p < 0.05$). By considering the completion time measure (see Figure 12), we observe that partners of this group has more difficulties to find targets than the two other groups. Figure 15 shows that the mean force applied by the two partners, which highlights the fastness and the

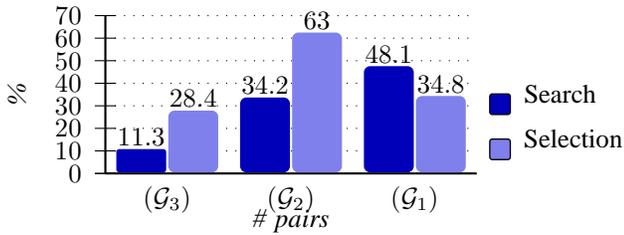


Figure 14: Percentage of verbal communication during searching and selection steps: Pairs working in close regions are more efficient for the selection task. Conversely, pairs working in distant and neighbouring regions are more efficient for the search task.

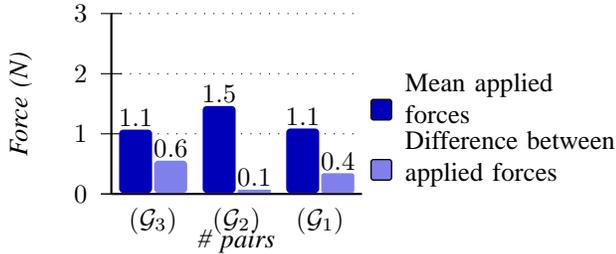


Figure 15: Mean applied force between the two partners: Results show that an important applied force enables a better control of manipulated structures, and a low applied forces enables a gesture guidance.

amplitude of movements during the manipulation, is similar with group 3 but is lower with a significant difference with group 2 ($p < 0.05$). The difference of applied forces, which reflects the level of coordination between the two partners, is intermediate compared to the two other groups.

Based on these results we can conclude that working on the same region (e.g., same residue), which concerns partners with an important affinity, provides intermediate improvement in term of completion time, level of coordination and verbal communication.

2) *Group 2*: From Figure 10, we observe that this group presents an intermediate distance between the two workspaces of partners ($8 \text{ cm} < \text{distance} < 14 \text{ cm}$). This distance is at the scale of two or three residues ($10 \text{ \AA} < \text{distance} < 20 \text{ \AA}$) which mean that partners worked on connected residues (structural dependency) or close residues belonging to two close macrostructures (physical dependency) (see Figure 16). Around 1/3 of pairs adopt this working strategy that involves important physical and structural coupling between the manipulated regions.

From Figure 11, we observe that this configuration of work concerns partners with an average affinity but with high skills. This group includes mainly colleagues with hierarchical links (e.g. students with their supervisors) and biological experts. Figure 12 shows that this group presents the best total completion time compared to the two other groups. Moreover, we observe a low level of communication between partners (see Figure 13). Figure 14 shows that this group dedicates more communication time for the selection than for the search ($p < 0.05$). By considering the completion time (see Figure 12), we observe that this group find rapidly

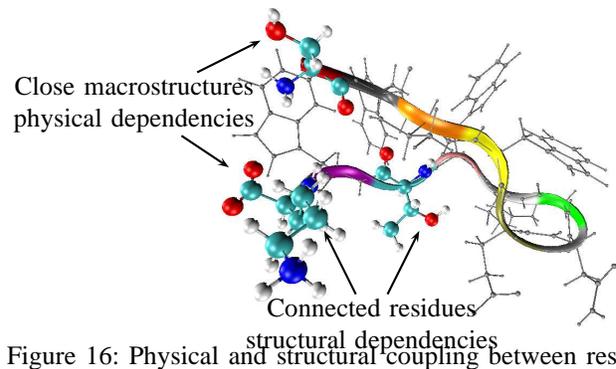


Figure 16: Physical and structural coupling between residues (TRP-CAGE molecule).

targets compared to the two other groups. Figure 15 shows that this group present the more faster movements with the largest amplitudes during the manipulation. Moreover, the low difference of applied forces highlights the high level of coordination between partners.

Based on these results we can conclude that working on neighboring regions (e.g., connected residues, close residues belonging to close macrostructures), which concerns partners with a medium affinity, provides the best performances in term of completion time, level of coordination and verbal communication.

3) *Group 3*: From Figure 10, we observe that this group presents the most important distance between the two workspaces of partners (distance $> 14 \text{ cm}$). It means that partners manipulate structures presenting low or no physical and structural coupling ($20 \text{ \AA} \ll \text{distance}$). This minor strategy (one pair among 12) involves a low interaction between partners since they work on different workspaces. From Figure 11, we observe that this configuration of work concerns partners with no particular affinity and who do not know the other one. Figure 12 shows that this group presents the most important completion time compared to the two other groups. From Figure 13 and Figure 12, we observe that this group communicate less than the two other groups (ratio between communication and completion time). Moreover, we observe that this group does not communicate much during the search step (see Figure 14). Once the target found, they communicate slightly more to select together the target. Figure 15 shows that this group presents medium gestures speed and amplitude. Moreover, the important difference of applied forces highlights the low level of coordination between partners.

Based on these results we can conclude that working on distant regions (e.g., structures presenting no physical or structural coupling), which concerns partners with no affinity, provides bad performances in term of completion time and level of coordination. Moreover, the level of communication is very low which highlights the low level on interaction between partners.

C. Qualitative results

The results from the questionnaire show that the majority of participants prefer and appreciate the collaborative configuration (mean score on the 5-point Lickert scale of 4.6 ± 0.5).

Moreover, the feeling of doing a collaborative task is important. Each participant considers that he contributes effectively to task fulfilment (mean of 4.1 ± 0.9). However, the proposed tasks do not lead to the impression of a leader/assistant configuration (mean of 3.0 ± 0.6). In fact, additional questions reveal that a large proportion ($\approx 70\%$) of participants tend to overestimate the role of the partner.

With respect to communication between partners, the answers highlight the role and the efficiency of verbal communication for the global coordination of the tasks (mean of 4.5 ± 0.6). The display of the VEE has a secondary role in the communication process (mean of 3.5 ± 0.8). It enables the designation of the ROI or the understanding of the partner's working space. However, participants highlight some difficulties to view and understand the low amplitude of the partner's movements (VEE) during close manipulation. In addition to the complexity of the molecular environment and the limits of 3D perception, this limit in awareness is due to the physical absence of the partner from the virtual environment. In fact, in addition to displaying the hands (VEE), the representation of the body plays an important role in understanding the associated gestures.

The participants' real gestures are of no significant help for communication (mean of 1.5 ± 1.0). In fact, the distance between the virtual scene (large screen, VEE, etc.) and the participants inhibits this communication channel. Our observations show that the participants focus on the virtual scene which corresponds to the direct observations of the partner. The standard face-to-face communication scheme is used in the case of a lack of understanding and conflicting situations.

VI. SYNTHESIS OF RESULTS

Based on all developed results, we can consider that **H1** is validated for complex tasks only. This type of tasks requires a strong collaboration between the two partners which leads to an improvement of performance compared to the single user configurations. Tasks presenting a low level of complexity do not require a collaboration and one participant can achieve effectively the task.

In addition, the results highlight three different working configurations. We can consider that **H2** is validated. Table I summarizes the different features of highlighted working configurations.

From these results, we observe that the most optimal configuration corresponds to partners working on neighbouring regions which correspond to connected residues (structural dependency) or close residues belonging to two close macrostructures (physical dependency). We can suppose that this working configuration enables the most suitable association and complementarity between the actions of the two partners.

From all results, we can summarize the main involved factors for the collaborative search of targets in the following points:

- **Participants' skills** This expresses both the understanding and interaction with 3D environments, and the biological skills required to understand and control the molecular structure and to know which are relevant zones (flexible zone, high energy zone, etc.).
- **Affinity between partners** This defines the way in which partners communicate and work together (e.g. working space, task dependency, etc.).
- **Task features** This includes both the nature of the task (i.e. search or deformation), and the complexity of the task (e.g. internal structure, noticeable structure, common structure, etc.).

VII. CONCLUSION AND PROSPECTS

This study highlights the role of collaboration between two participants for the fulfilment of a complex task. The results revealed that the efficiency of teamwork is linked to several human and task factors. We observe that the contribution of collaboration is more important when tasks are more difficult. The different pairs collaborate through different strategies. The study reported here has highlighted the role of communication during collaboration and the limits of communication through virtual and complex environments. It is worth mentioning that after exploring the collaborative search process, our next step, will be to investigate collaborative deformation and assembly procedures. In fact, these tasks involve different constraints and require closely coupled manipulation of structures. Moreover, for these studies, we will consider new measures and analysis approaches to highlight high level behaviors. For instance, a video recording coupled with annotations of partners actions will highlight actions (gestural, verbal, etc.) of subjects in the real environment and their consequences in the virtual environment (working strategies, efficiency, etc.). Beyond pairs of participants, we will investigate configurations with more participants in order to highlight, the evolution of group organizations, conflicts and the communication process.

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Table I: Features of the different working strategies

Distance	Completion time	Verbal communication	Level of coordination	Affinity
Same region	Medium	Medium	Medium	High
Neighbouring regions	High	Low	High	Medium
Distant regions	Important	Low	Medium	No

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